Complete Summary

GUIDELINE TITLE

Guidance on the use of imatinib for chronic myeloid leukaemia.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of imatinib for chronic myeloid leukaemia. London (UK): National Institute for Clinical Excellence (NICE); 2003 Oct. 26 p. (Technology appraisal; no. 70).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- October 19, 2006 – Gleevec (imatinib mesylate): Revisions to the PRECAUTIONS section of the prescribing information, describing the occasional occurrence of severe congestive heart failure and left ventricular dysfunction in patients taking Gleevec.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic myeloid leukemia (CML)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Internal Medicine
Oncology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost-effectiveness of imatinib in the treatment of chronic myeloid leukemia

TARGET POPULATION

Patients with Philadelphia-chromosome-positive chronic myeloid leukemia (CML) in chronic phase

INTERVENTIONS AND PRACTICES CONSIDERED

Imatinib mesylate (STI-571, Gleevec® or Glivec®)

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Quality of life
    - Overall survival
    - Hematological and cytogenetic response
    - Adverse effects
- Cost-effectiveness and cost-utility

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group, University of Exeter and Wessex Institute for Health Research and Development, University of Southampton (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Search Strategy

Three separate searches of electronic databases were performed to identify published studies and ongoing research (see Appendix 10.3, page 90 of the Assessment Report [see the "Availability of Companion Documents" field]).

Imatinib

The search performed for the previous NICE assessment report on imatinib as second line treatment for chronic myeloid leukaemia (CML) was updated. The previous strategy identified studies assessing first line treatment of CML. The search was not restricted by study design.

Interferon (INF) Alpha versus Hydroxyurea (HU)

The Assessment Group updated the previous NICE assessment report search for the comparison of HU and IFN-alpha. This search was restricted to randomized comparisons, as high-level evidence is known to exist.

Interferon Alpha versus Bone Marrow Transplant (BMT)

The Assessment Group conducted searches to identify evidence for BMT versus IFN-alpha. No restrictions by date of publication were applied to this search.

All searches were restricted to English language and the search terms and strategy are outlined in Appendix 10.3 (page 90 of the Assessment Report [see the "Availability of Companion Documents" field]). Bibliographies of identified publications were searched for further relevant articles, handsearching of

conference abstracts (European Haematology Association, American Society of Clinical Oncology, International Society for Experimental Hematology, and American Society for Hematology) for imatinib was performed, and the manufacturers of imatinib were approached for unpublished studies.

Inclusion and Exclusion Criteria

Two independent researchers reviewed titles and abstracts for inclusion. The full text of articles deemed relevant were obtained and the two researchers independently reviewed each for final inclusion. Disagreements were resolved by consensus.

The following inclusion criteria were applied:

Study Design

- Imatinib compared to any other treatment: studies with a control group only
- IFN-alpha compared to HU: randomised controlled trials only
- IFN-alpha compared to BMT: studies directly comparing IFN-alpha and BMT in the same study only

Stricter study design criteria were applied to comparison of IFN-alpha and HU due to the large number of randomised trials known to be available.

If studies were reported only in abstract form the Assessment Group tried to obtain the full text article. If a full text article was not available the abstract was excluded.

Population

Adults presenting for first line treatment of CML in chronic phase were included. Studies of patients in accelerated or blast phases were excluded.

Intervention and Comparisons

Studies comparing the following were included:

- Imatinib compared to any other treatment
- IFN-alpha compared to HU
- IFN-alpha compared to BMT

Studies of HU were only included if at least 75% of the control group received HU (e.g., at least 75% received HU and up to 25% received other agents such as busulphan [BU]). Relevant meta-analyses were only included if they reported all relevant outcomes that were present in the original reports of the randomised controlled trials (RCTs), otherwise the original RCTs were included.

Outcomes

Quality of life, overall survival, haematological response, cytogenetic response, and adverse effects were included.

Cost Effectiveness

Electronic databases were searched for published economic studies. The economic search performed for the previous NICE assessment report on imatinib as second line treatment for CML was updated. All economic studies of any treatment for chronic phase CML in adults have been included.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

Imatinib

No studies of imatinib identified in the previous National Institute for Health and Clinical Excellence (NICE) assessment report were included in this report as they all considered second line treatment of chronic myeloid leukaemia (CML).

The update search identified a total of 213 articles, one of which was included after completing the selection process.

Interferon (IFN)-alpha Compared to Hydroxyurea (HU)

Four randomised controlled trials (RCTs) were included from the previous NICE assessment. Two of the RCTs from the previous assessment report were excluded as more than 25% of the control groups received busulphan. In addition, the one published meta-analysis was excluded as more complete documentation of relevant outcomes was included in individual trial reports.

The additional update search failed to identify any new relevant RCTs.

IFN-alpha Compared to Bone Marrow Transplant (BMT)

A total of 339 articles were identified of which five non-randomised comparative studies met the inclusion criteria.

Cost-Effectiveness

Only one published abstract of an economic evaluation of imatinib was identified, along with three published economic evaluations of IFN-alpha, and two published evaluations of BMT.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Peninsula Technology Assessment Group, University of Exeter and Wessex Institute for Health Research and Development, University of Southampton (see the "Availability of Companion Documents" field.)

Data Extraction Strategy

Data were extracted by one reviewer and checked by a second reviewer. Response rates and survival were calculated where possible from original data presented in the reports and not from percentages given in the report, which are often adjusted for a variable number of dropouts. In some cases, survival was estimated from survival curves presented in the results.

Quality Assessment Strategy

Using a structured form, the internal and external validity of the included studies were assessed by one researcher and checked by a second. The quality assessment of comparative studies was based on the following criteria:

Randomised controlled trials (RCTs)/comparative studies (Center for Reviews and Dissemination [CRD] Report No. 4)

- Was the assignment to treatment groups an adequate method of randomisation?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were the outcome assessors blinded to the treatment allocation?
- Was the care provided blinded?
- Was the patient blinded?
- Were point estimates and measure of variability presented for the primary outcome measure?
- Was the analysis intention-to-treat?

The external validity was reviewed through consideration of patient characteristics including eligibility and inclusion/exclusion criteria.

Data Synthesis

Due to the lack of suitable randomised evidence, meta-analyses have not been performed. Data are described through narrative and summarised in tables.

No direct evidence comparing imatinib with hydroxyurea (HU) or bone marrow transplant (BMT) was identified. The Assessment Group has therefore calculated outcome measures directly from the relevant single arms of available trials to enable an approximate assessment of the efficacy of Imatinib in relation to these treatments. It cannot be emphasised too strongly that this kind of comparison is potentially biased, particularly in terms of potential differences in the populations studied, the variable completeness of follow-up, publication bias.

A further difficulty arises from the short-term follow-up in the imatinib trial and the consequent reliance on haematologic response (HR) and cytogenetic response (CR) as proxy outcome measures for longer-term survival.

When 95% confidence intervals were not described in the original reports, these have been calculated wherever possible using STATA™.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Only one published abstract concerned with economic evaluation of second-line imatinib therapy (after interferon [IFN]-alpha had failed) was identified in the literature. In addition, the manufacturer's submission presented an economic model, and the Assessment Group developed an independent economic model.

The published economic evaluation (abstract only) did not provide full details of methodology or sensitivity analyses. This study reported the incremental cost-effectiveness ratio (ICER) of imatinib as a second-line treatment over hydroxyurea (HU) in the chronic phase to be 35,000 pounds sterling per quality-adjusted life year (QALY). The ICER for imatinib compared with combination chemotherapy or palliative care in the accelerated phase was around 22,000 pounds sterling per QALY and in the blast-crisis phase 43,500 pounds sterling per QALY. The year of costs was not stated but the abstract was presented in 2002.

The manufacturer's submission included an economic evaluation based on a new Markov model that compared the costs and QALYs in a hypothetical cohort of 1000 newly diagnosed people receiving imatinib as a first-line treatment with a similar cohort of 1000 people receiving IFN-alpha. The model runs for 30 years, using 1-month cycles. The key effectiveness data were based on the IRIS study. Using two different techniques to estimate the survival benefit, the manufacturer's

model estimated that the ICERs for imatinib treatment when compared with IFN-alpha were 19,000 pounds sterling and 27,000 pounds sterling per QALY.

An independent economic model was developed by the Assessment Group to determine the ICER of imatinib compared with HU and IFN-alpha, and of IFN-alpha compared with HU in terms of cost per QALY. This is a Markov model that follows a cohort of 1000 people with chronic myeloid leukaemia (CML) from the start of treatment until death, or for a maximum of 20 years. The cycle length for the model is 3 months and costs are calculated based on a National Health Service (NHS) perspective. Key effectiveness data comes from published literature.

The independent model estimated the ICER of imatinib compared with IFN-alpha to be around 26,000 pounds sterling per QALY gained (ranging from 13,500 pounds sterling to 52,000 pounds sterling). Results were relatively robust when subjected to a number of sensitivity analyses. The highest ICER estimate was obtained when higher doses of imatinib were assumed (that is, 600 mg for the chronic and accelerated phases and 800 mg for the blast-crisis phase). Imatinib was less cost effective when compared with HU, with an ICER of 87,000 pounds sterling per QALY. The ICER of IFN-alpha when compared with HU was considerably higher – in excess of 1 million pounds sterling per QALY.

In the Institute's previous guidance (*National Institute for Clinical Excellence [NICE] Technology Appraisal Guidance* No. 50), the ICER for imatinib treatment when compared with HU was estimated to be between 36,000 pounds sterling and 38,000 pounds sterling per QALY as a second-line treatment in chronic-phase CML, between 21,800 pounds sterling and 56,000 pounds sterling per QALY in the accelerated phase, and between 33,275 pounds sterling and 64,750 pounds sterling per QALY in the blast-crisis phase.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Imatinib is recommended as first-line treatment for people with Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in the chronic phase.
- Imatinib is recommended as an option for the treatment of people with Philadelphia-chromosome-positive CML who initially present in the accelerated phase or with blast crisis. Additionally, imatinib is recommended as an option for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.
- There is currently no evidence on clinical and cost effectiveness on which to base guidance on the continued use of imatinib that has been initiated in the chronic phase of CML but has failed to stop disease progression to either the accelerated phase or blast crisis. Therefore, under these circumstances the use of imatinib is recommended only in the context of further clinical study. The data for this study should be collected systematically to allow aggregation and analysis at a national level in order to inform the appraisal review.
- For people in chronic-phase CML who are currently receiving interferon alpha (IFN-alpha) as first-line treatment, the decision about whether to change to imatinib should be informed by the response of the disease to current treatment and by the tolerance of the person to IFN-alpha. This decision should be made after informed discussion between the person with CML and the clinician responsible for treatment, taking full account of the evidence on the risks and benefits of imatinib and the wishes of the person.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of imatinib in patients with chronic myeloid leukemia

POTENTIAL HARMS

The majority of people taking imatinib experience adverse reactions at some stage. The most frequently reported adverse effects of imatinib in clinical studies include nausea, vomiting, edema (fluid retention), muscle cramps, skin rash, diarrhea, abdominal pain, headache and fatigue. Cytopenia, particularly neutropenia and thrombocytopenia, has been reported in all studies, with a higher incidence in people in blast crisis and in the accelerated phase compared with

those in the chronic phase. In clinical studies, 1% of people in the chronic phase, 2% of those in the accelerated phase, and 5% of those in the blast-crisis phase were withdrawn because of adverse events.

For full details of side effects and contraindications, see the summary of product characteristics (SPC) available at http://emc.medicines.org.uk/.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- All clinicians who treat people with chronic myeloid leukaemia (CML) should review their current policies and practice in line with the guidance set out in the "Major Recommendations" field.
- Local guidelines or care pathways for the care of patients with CML should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - Imatinib is provided as first-line treatment for the management of an individual with Philadelphia-chromosome-positive CML in the chronic phase.
    - Imatinib is considered as an option for the treatment of an individual with Philadelphia-chromosome-positive CML who initially presents in the accelerated phase or in blast crisis or who presents in the chronic phase and then progresses to the accelerated phase or blast crisis if he or she has not received imatinib previously.
    - For an individual in chronic-phase CML who is currently receiving interferon (IFN)-alpha as first-line treatment, the decision to change to imatinib is informed by the response of the disease to current treatment and the individual's tolerance of IFN-alpha, after informed discussion between the individual and the clinician responsible for treatment.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Guidance on the use of imatinib for chronic myeloid leukaemia. London (UK): National Institute for Clinical Excellence (NICE); 2003 Oct. 26 p. (Technology appraisal; no. 70).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Oct

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Imatinib for chronic myeloid leukaemia. Summary. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep. 2 p. (Technology appraisal 70). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- The effectiveness and cost-effectiveness of imatinib for first line treatment of chronic myeloid leukaemia in chronic phase. NHS R&D HTA programme.

Peninsula Technology Assessment Group, Exeter, UK. 2003 Mar 28. 146 p. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0336. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Imatinib for chronic myeloid leukaemia. Understanding NICE guidance – information for people with chronic myeloid leukaemia, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Oct. 10 p. (Technology appraisal 70).

Electronic copies: Available in English and Welsh in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N0337. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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